9 | LYSERGIC ACID DIETHYLAMIDE

Lysergic acid diethylamide (LSD) is a highly potent, hallucinogenic drug. Considered to be one of the most powerful drugs available, typical doses of LSD fall between 20 and 100 μg (A. J. Jenkins, 2013; Khan, Kennedy, & Christian, 2012; NDIC, 2004a). Historically, LSD was dissolved into sugar cubes or gelatin squares before being sold to those seeking psychedelics (*The Army Lawyer*, 1991); however, in 1991, the United States determined that the "carrier" LSD was dissolved into or onto was part of the drug mixture, and therefore the carriers weight (i.e., the weight of the sugar or gelatin) counted toward the overall drug weight, increasing the severity of criminal punishment (Chapman v. United States, 1991). Because of this, clandestine laboratories shifted away from dissolving LSD on sugar cubes and opted for a carrier with less weight. Currently, LSD is most commonly found impregnated in blotter paper or pressed into pills, though it can also be impregnated into postage stamps or lick-and-stick tattoos (A. J. Jenkins, 2013; NDIC, 2004a; OBNDD, n.d.).

Due to effects being elicited with as little as 25 μg of LSD, and the possibility for overdose-related convulsions after administration of 2 mg, law enforcement processing a clandestine LSD laboratory should don Level A PPE, including fully encapsulated, air tight suit with SCBA (NCBI, n.d.-b; Emergency Management Australia, 2000; NES, 2019; Pacsial-Ong & Aguliar, 2013). Dermal absorption of LSD has not been well characterized, but LSD can be aerosolized, leading to the potential of an inhalational exposure (Rega, 2019). Once LSD enters the body, regardless of the route of exposure, it is completely absorbed and concentrates in the portions of the brain responsible for visions, leading to hallucinations and psychosis within 5–20 min and lasting as long as 12 hr (A. J. Jenkins, 2013).

When processing a clandestine LSD laboratory, the laboratory should not be ventilated unless the surrounding area is evacuated and the acting environmental protection agency is notified (DEA, 2005). Ventilation of the laboratory can cause unwanted environmental contamination from LSD, as well as the precursor materials, some of which are hazardous, such as hydrazine (carcinogen) and ethyl iodide. Additionally, ventilation of an LSD laboratory can cause release of the *Claviceps purpurea* fungus, which is considered a mycotoxin (Richard, 2007). LSD is classified as a potential incapacitation chemical weapon, so aerosolization should be avoided if possible (Emergency Management Australia, 2000; Pacsial-Ong & Aguliar, 2013; Polat, Gunata, & Parlakpinar, 2018). If an exposure occurs, there is currently no known LSD antagonist; those exposed should be treated with diazepam to sedate them until the LSD is cleared from the body (Emergency Management Australia, 2000).

9.1 | Alkaloid isolation

Unlike many drugs synthesized in clandestine laboratories, the synthesis of LSD is rather difficult and time consuming; the synthesis takes several days to complete, and requires a laboratory to have advanced chemistry knowledge and equipment (Cooper, 1988; EMCDDA, n.d.-b; Garbrecht, 1959; Kornfeld et al., 1956; Z. Li et al., 1997). While there are several routes of synthesis for LSD, most of them require naturally occurring alkaloids as starting materials, including ergine, ergonovine, and ergotamine (Laing, 2003). These alkaloids can be extracted from morning glory and baby woodrose seeds, though these two plants are not a preferred method of obtaining the alkaloids, as they contain small amount of alkaloids and are expensive (Hoffer, 1965). The preferred route of obtaining the alkaloids is through ergot

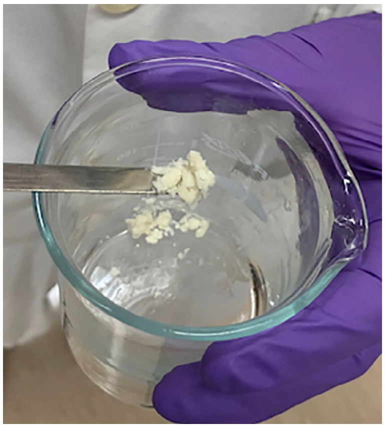

FIGURE 38 Crack cocaine produced with the microwave method

infested rye. Rye infected with *Claviceps purpurea* form a dark brown/purple sclerotium, which is a hardened fugal mass containing the alkaloids of interest (Richard, 2007). In a clandestine LSD laboratory, the sclerotium is harvested from the infected rye, dried, then ground up and soaked in an organic solvent, such as ether, hexane, or naptha, removing the fatty acids (Laing, 2003). Once the fatty acids have been removed, the remaining powder is washed with an organic solvent made alkaline with a base, such as chloroform mixed with ammonium hydroxide. The washing solvent is collected and allowed to evaporate, leaving behind a mixture of alkaloids. To isolate the lysergic acid alkaloid, the mixture of alkaloids is dissolved in a tartaric acid solution, which is combined with chloroform in a separatory funnel. The solution is made alkaline through the addition of sodium bicarbonate and then mixed. Following mixing, the two layers are allowed to separate and the chloroform layer is collected, the chloroform is evaporated, and the resulting lysergic acid-containing, ergot alkaloids can be collected (Valentine Smith, n.d.); for a list of natural and semisynthetic ergot alkaloids and their structure, see Sibley et al.'s chapter in *Goodman & Gilman's: The Pharmacological Basis of Therapeutics* (Sibley, Hazelwood, & Amara, 2017).

9.2 | LSD synthesis

Once the lysergic acid alkaloid is isolated, it must be protected from the elements, as it can quickly degrade due to UV light, oxygen, heat, and pH (Z. Li, McNally, Wang, & Salamone, 1998). To combat degradation of the LSD precursors and products, many of the reactions are carried out under red or yellow dark room lights with reaction vessels wrapped in aluminium foil, in inert atmospheres, and in temperature-controlled baths (Laing, 2003; Z. Li et al., 1997, 1998; A. Shulgin & Shulgin, 2002; Valentine Smith, n.d.). Typically, 1 of 10 common routes are used to convert the ergot alkaloids to LSD (Laing, 2003):

- Azide
- Carbonyldiimidazole
- Dicyclohexylcarbodiimide
- Dicyclohexylcarbodiimide hydroxybenzotriazol
- Oxalyl chloride
- Phosgene
- Phosphoryl chloride
- Sulfur trioxide
- Thionyl chloride
- Trifluoroacetic anhydride

These 10 routes fall into four classifications, based on the intermediate product formed during synthesis: acid chloride, azide, imidazole, and mixed anhydride (Laing, 2003); an example of each classification is outlined below.

9.2.1 | Azide method

Of the various routes of LSD synthesis, the azide method, patented by Arthur Stoll and Albert Hofmann in 1948, is the most popular route Figure 39. To synthesize LSD via the azide method, the alkaloid ergotamine is cleaved with anhydrous hydrazine, resulting in lysergic acid hydrazide. The lysergic acid hydrazide is then treated with sodium nitrite under acidic conditions to give lysergic acid azide. The azide compound can then be mixed with diethylamine to give LSD with a 69% yield, 80% of which is the normal, active form and 20% of which is the iso-form (Laing, 2003; Nelson & Foltz, 1992; Stoll & Hofmann, 1948).

9.2.2 | Carbonyldiimidazole method

The carbonyldiimidazole method for LSD synthesis was published by in 1962 and the reaction pathway is shown in Figure 40 (Černý & Semonský, 1962). *N*,*N*-carbonyldiimidazole is mixed with lysergic acid to give an imidazole intermediate, which is then mixed with diethylamine, forming LSD with an 81% yield (Laing, 2003). Not only does the carbonyldiimidazole method have a greater yield than the azide method, but it also results in fewer by-products and is not as sensitive to temperature fluctuations during the synthesis process (Černý & Semonský, 1962; Laing, 2003).

9.2.3 | Dicyclohexylcarbodiimide method

The dicyclohexylcarbodiimide (DCC) method (Figure 41) was originally developed by Sheehan and Hess in 1955 as a means to form peptide bonds through a condensation reaction of the carboxylic acid group of one amino acid and the amine group of another (Sheehan & Hess, 1955). This reaction was repurposed for the synthesis of LSD, where DCC is mixed with lysergic acid to give a DCC-lysergic acid intermediate. The DCC is then displaced by a second lysergic acid molecule, forming lysergic acid anhydride; the formation of this anhydride is not favored, resulting in the DCC method having a low yield of LSD (Laing, 2003).

The DCC method was modified in 1978 by Losse and Mahlberg, who added 1-hydroxybenzotriazole (HBOt) to the reaction (Losse & Mahlberg, 1978). This addition prevented the need to form the LSD anhydride, and instead formed a HBOt-lysergic acid intermediate. The addition of HBOt to the carboxylic acid makes it a good leaving group, and when the intermediate is mixed with diethylamine, LSD is formed with an 80% yield, though 66% is iso-LSD (AAPPTec, n.d.; Laing, 2003; *LSD Synthesis Using Peptide Coupling Reagents*, n.d.).

9.2.4 | Acyl chloride method

In the acyl chloride method, lysergic acid is combined with dimethylformamide and a chloride-containing compound to generate the acid chloride analogue of lysergic acid (Figure 42). The carbon of the resulting acyl chloride group is highly electropositive, causing it to be a favored point for nucleophilic attack (Afonso et al., 2016). When the lysergic acid chloride is mixed with diethylamine, the lone pair of electrons on the nitrogen create a bond with the acyl chloride carbon and the chloride is displaced, resulting in the formation of LSD. To date, four chloride-containing compounds have been extensively used in the synthesis of LSD: thionyl chloride, phosgene, phosphoryl chloride, and oxalyl chloride (Johnson, Ary, Teiger, & Kassel, 1973; Kenner & Stedman, 1952; Patelli & Bernardi, 1964; Ziegler & Stutz, 1985). The acyl chloride method results in yields as great as 66% that are predominately comprised of the normal isomer of LSD (Johnson et al., 1973; Laing, 2003; A. Shulgin & Shulgin, 2002).

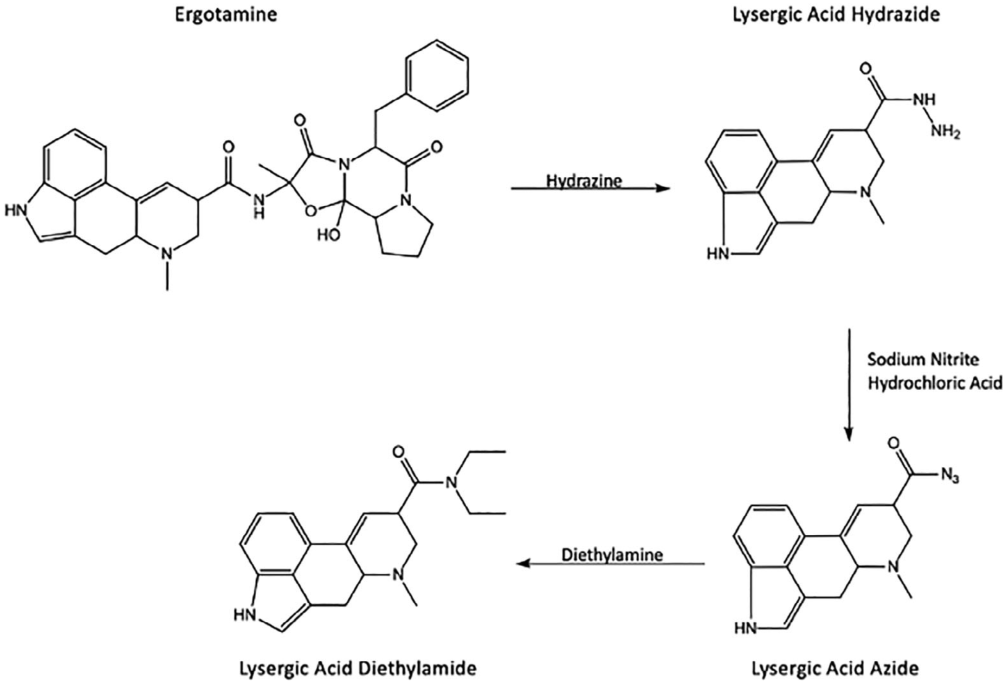

FIGURE 39 The azide method of LSD synthesis

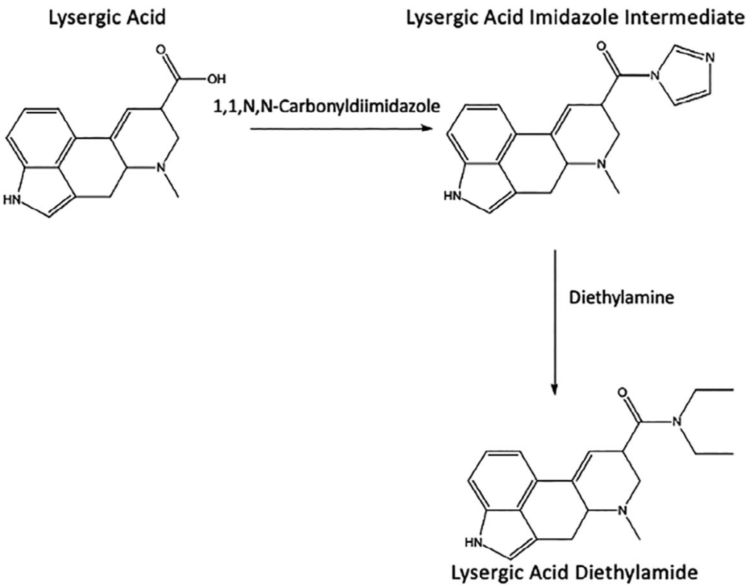
Lysergic Acid
1,1,N,N-Carbonyldiimidazole
Lysergic Acid Imidazole Intermediate
Diethylamine
Lysergic Acid Diethylamide

FIGURE 40 Carbonyldiimidazole method of LSD synthesis

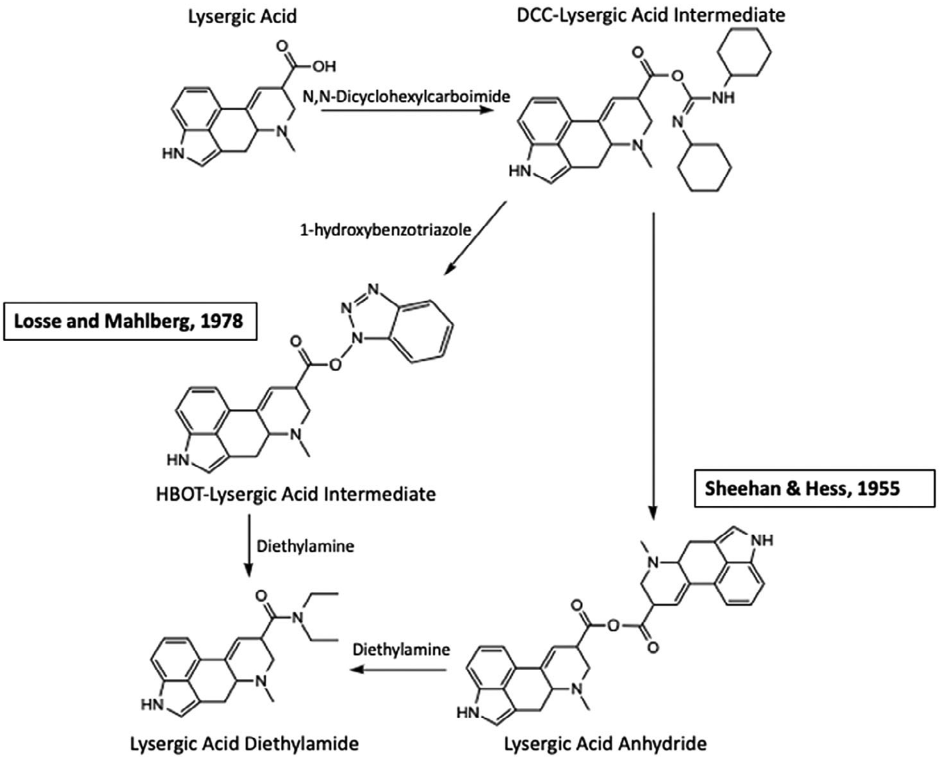

FIGURE 41 Two versions of the dicyclohexylcarbodiimide method of LSD synthesis

9.2.5 | Mixed anhydride method

In the mixed anhydride method, trifluoroacetic anhydride is mixed with lysergic acid at low temperatures (approximately −20°C). This reaction causes an adduct to form between the basic amine of the lysergic acid and the trifluoroacetic anhydride. A second trifluoroacetic anhydride then interacts with this adduct, forming the lysergic acid mixed anhydride (Figure 43) (Pioche, 1956). If this step of the reaction is not complete at low temperatures, the lysergic acid mixed anhydride will quickly degrade and the synthesis will be unsuccessful (Laing, 2003). To form LSD, the lysergic acid mixed anhydride is added to excess diethylamine; the presence of the excess basic nitrogens will cause the trifluoroacetic acid group to leave the anhydride, allowing diethylamine to bind and form LSD (Pioche, 1956). The mixed anhydride method forms LSD with a yield of 58%, though a large percentage of the resulting product is iso-LSD (Laing, 2003).

An alternate approach to the mixed anhydride method was patented by Garbrecht (1956). In Garbrecht's approach (Figure 43), lysergic acid is treated with lithium hydroxide to form lithium lysergate, which is then mixed with sulfur trioxide dimethylformamide to obtain the lysergic acid sulfur trioxide anhydride. The anhydride is then mixed with diethylamine to form LSD (Garbrecht, 1956, 1959). One advantage of Garbrecht's approach over Pioche's approach, is that the lysergic acid sulfur trioxide anhydride is not formed under acidic conditions like the lysergic acid trifluoroacetic anhydride is, preventing the sulfur trioxide anhydride from degrading as rapidly (Laing, 2003). Additionally, Pioche's trifluoroacetic anhydride approach resulted in non-specific acetylation of the lysergic acid molecule, resulting in numerous by-products in the LSD while Garbrecht's sulfur trioxide approach resulted in more specific acetylation of the carboxyl group (Garbrecht, 1959).

10 | PHENCYCLIDINE

Phencyclidine (PCP) was first synthesized and utilized as an anesthetic in 1956 by the Parke-Davis pharmaceutical company (Bertron, Seto, & Lindsley, 2018). By 1963, PCP was no longer marketed for human use, due to the adverse side-effects, including delusions, delirium, hallucinations, muscle rigidity, dysphoria, psychosis, and seizures (A. J. Jenkins, 2013). The first clandestine production of PCP was record in 1967 in San Francisco, CA (A. J. Jenkins, 2013). Abuse of the hallucinogen has come and gone in waves, with increased use seen in the 1970s, 1990s, and the latter half of the 2010s (Dew et al., 2017; A. J. Jenkins, 2013; Nishida, 2014). Locations of PCP abuse tend to be regionalized to larger metropolitan areas of the United States, including Los Angeles, New York, Washington D.C., Houston, Baltimore, and Philadelphia, where it is primarily synthesized and distributed by the Bloods and Crips street gangs (A. J. Jenkins, 2013; Murray, 2020; NDIC, 2004b; Nishida, 2014); PCP abuse has not been prominent outside the United States (J. P. Jenkins, 2019; UNODC, n.d.-a).

Over the years, there have been numerous synthetic routes published for the production of PCP, though the most commonly encountered route in clandestine laboratories is known as the "bucket method" (Bertron et al., 2018; Frank, 1983; Khan et al., 2012; Maddox, Godefroi, & Parcell, 1965; A. T. Shulgin & MacLean, 1976). The bucket method of PCP synthesis is simple to perform and requires no heating or sophisticated laboratory equipment, but is considered a high-hazard laboratory due to the possibility of cyanide production and the high lipophilicity of PCP itself (Armenian, 2012; Bertron et al., 2018; Blauser, 2017; NES, 2019). PCP is readily absorbed from all routes of administration, including through the skin, and quickly concentrates in the fatty tissues of the body, including the brain (Armenian, 2012; NIDA, 1986). Psychosis can occur following ingestion of 6–10 mg of PCP, and death can occur following ingestion of 150–200 mg (Armenian, 2012).

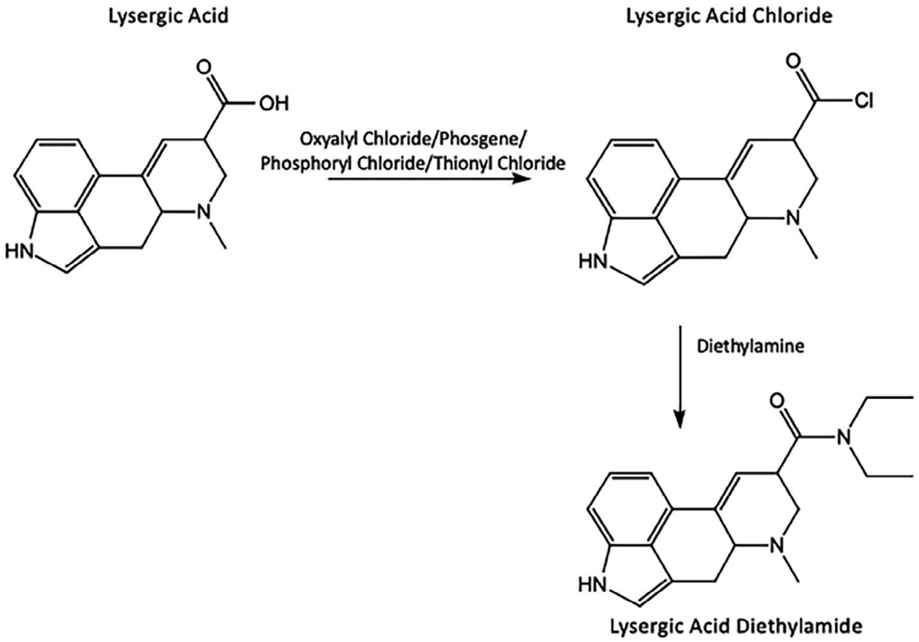
Lysergic Acid
O
OH
HN
N
Oxyalyl Chloride/Phosgene/
Phosphoryl Chloride/Thionyl Chloride
Lysergic Acid Chloride
O
Cl
HN
N
Diethylamine
O
N
HN
N
Lysergic Acid Diethylamide

FIGURE 42 The acyl chloride method of LSD synthesis

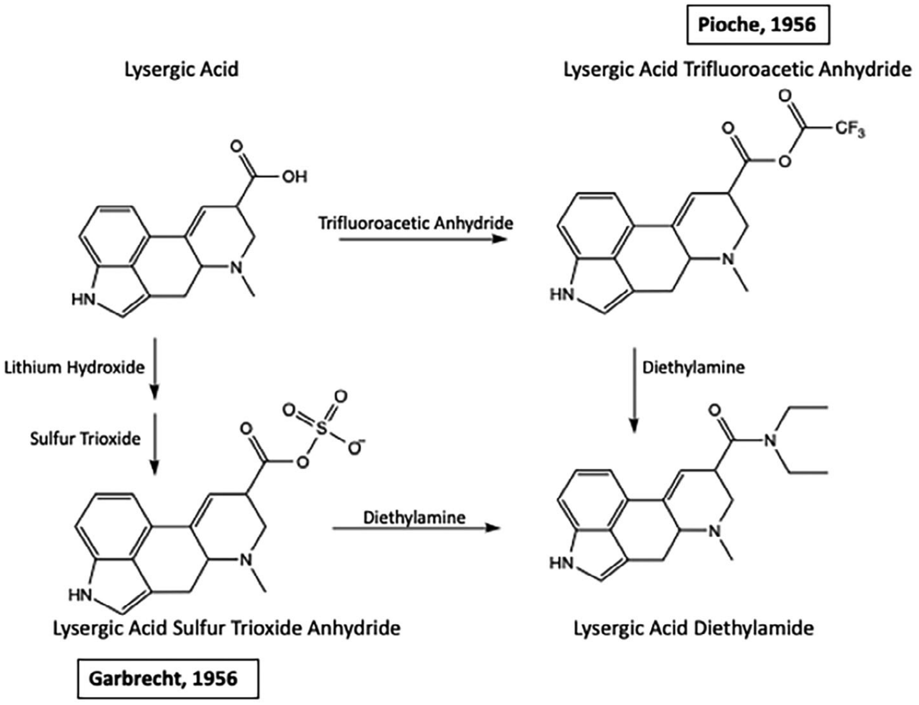
Pioche, 1956
Lysergic Acid
Lysergic Acid Trifluoroacetic Anhydride
OH
CF3
HN
N
Trifluoroacetic Anhydride
Lithium Hydroxide
Sulfur Trioxide
Diethylamine
Diethylamine
Lysergic Acid Sulfur Trioxide Anhydride
Lysergic Acid Diethylamide
Garbrecht, 1956

FIGURE 43 Two versions of the mixed anhydride method of LSD synthesis

Because of PCPs ability to be quickly absorbed and its toxicity, it is recommended that a clandestine PCP laboratory be processed in Level A protection, including an air-tight, fully encapsulated suit and SCBA (Armenian, 2012; Blauser, 2017; NES, 2019).

As the name suggests, a PCP bucket laboratory is a series of reactions, each of which is performed in its own bucket (Figure 44) (Angelos, Raney, Skowronski, & Wagenhofer, 1990; Cone, Vaupel, & Buchwald, 1980; Frank, 1983; Khan et al., 2012). The first bucket is used to synthesize the PCP precursor 1-piperidinyl cyclohexanecarbonitrile (PCC). While PCC can be purchased, it is a controlled substance in the United States, and is therefore more likely to be synthesized clandestinely than purchased (DEA, 2020b). To synthesize PCC, piperidine and ice-cold water are added to the bucket followed by hydrochloric acid, forming piperidine-HCl. Next, cyclohexanone is added, followed by potassium or sodium cyanide and the mixture is stirred for 4–8 hr, yielding 85–90% PCC (Khan et al., 2012; Laing, 2003). PCC is highly unstable, and is known to release cyanide through thermal elimination, even at temperatures as mild as room temperature (Allen, Robles, Dovenski, & Calderon, 1993; Ballinger & Marshman, 1979). Because of this, chemists processing a PCP laboratory should not immediately ventilate the scene due to the potential for releasing cyanide gas into the surrounding area.

The second bucket used for PCP synthesis is for preparation of the aryl Grignard reagent. To do this, magnesium turnings are added to the bucket, followed by ether. Then bromobenzene is added dropwise and the bucket is cooled as needed, resulting in the formation of phenylmagnesium bromide (Grignard reagent) (Khan et al., 2012). Sometimes crystal iodine is added during addition of the ether to initiate the formation of the Grignard reagent (A. T. Shulgin & MacLean, 1976). As with PCC, phenylmagnesium bromide can be purchased commercially, but is commonly produced clandestinely to prevent drawing the attention of law enforcement (A. T. Shulgin & MacLean, 1976).

The third bucket is for the synthesis of PCP. The PCC formed in the first bucket is added to the third bucket, along with additional ether. The Grignard reagent prepared in the second bucket is then slowly added to the third bucket, and the mixture is allowed to react for 2–3 hr (Allen et al., 1993; Angelos et al., 1990; Ballinger & Marshman, 1979; Frank, 1983; A. T. Shulgin & MacLean, 1976). During the reaction of PCC and the Grignard reagent, the nucleophilic attack occurs at the alpha carbon and not at the carbon of the cyanide group as normally occurs during Grignard reactions; this is due to the electron deficiency of the alpha carbon (Allen et al., 1993; Maddox et al., 1965; Yoshimura, Ohgo, & Sato, 1964). The bucket method has been reported to have an overall yield of greater than 73% (Bertron et al., 2018).

PCC is commonly found in seized PCP samples, as both have similar solubility properties and can be difficult to separate during the purification process (Ballinger & Marshman, 1979); PCC can make up over 20% of a seized PCP sample